

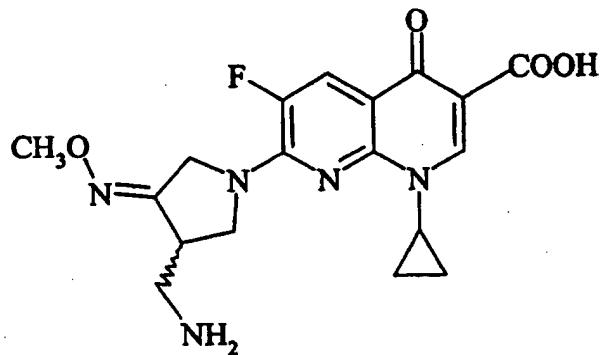
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PATENT & TRADEMARK OFFICE

PROCESS FOR PRODUCTION OF NAPHTHYRIDINE-3-CARBOXYLIC ACID DERIVATIVES

This application claims the benefit of U.S. Application No. 10/070,281, filed May 21, 2002, which is a National Stage 371 of PCT/GB00/03366, filed September 1, 2000, which claims priority to GB 9920917.3, filed September 3, 1999.

The present invention relates to a novel process for the production of pharmaceutically active compounds, for example, quinolone carboxylic acid derivatives having antibacterial activity.

EP 688772 discloses novel naphthyridine carboxylic acid derivatives having antibacterial activity, including anhydrous (R,S)-7-(3-aminomethyl-4-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid of the formula:



WO 98/42705 discloses (R,S)-7-(3-aminomethyl-4-syn-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate and hydrates thereof including the sesquihydrate.

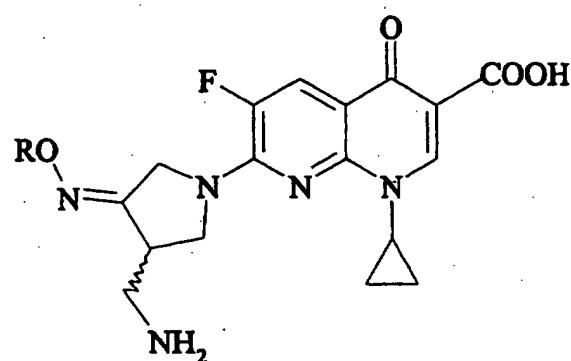
EP 688772 discloses a process for the production of (R,S)-7-(3-aminomethyl-4-syn-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid which comprises the reaction of 7-chloro-1-cyclopropyl-

6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid and 4-aminomethyl-3-methoxyiminopyrrolidinium ditrifluoroacetate in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene using dry acetonitrile as solvent. PCT/KR99/00099 (published after the priority date of the present application) discloses the same process using 4-aminomethyl-3-methoxyiminopyrrolidinium dihydrochloride.

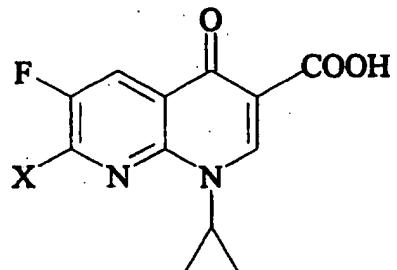
The present invention relates to an improved process for the production of quinoline carboxylic acid derivatives having antibacterial activity.

Thus according to the invention there is provided a process for the production of a compound of formula (I), or a pharmaceutically acceptable salt and/or hydrate thereof:

(I)

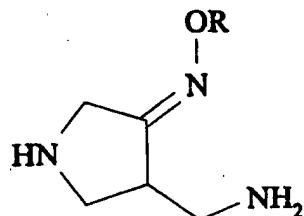


wherein R is C₁₋₄ alkyl or C₁₋₄ haloalkyl, which comprises reaction of a compound of formula (II):



(II)

wherein X is a leaving group; with a compound of formula (III):



(III)

wherein R is as defined for formula (I), or a salt thereof; in the presence of a base and an aqueous solvent;

and optionally forming a pharmaceutically acceptable salt and/or hydrate thereof.

Suitable aqueous solvents for use in the process according to the invention include aqueous acetonitrile and aqueous alcohols, e.g. aqueous C₁₋₆ alkyl alcohols such as aqueous ethanol; however the preferred solvent is water.

When the solvent used for the process is a mixed solvent any ratio of solvents may be used, for example when the solvent is aqueous acetonitrile a ratio of between 0.7 and 1.4 acetonitrile:water may be used, preferably 1:1 acetonitrile:water.

The reaction is preferably performed in greater than 1 volume of solvent based on the compound of formula (II), for example 10 volumes of solvent.

The reaction is preferably performed using an excess of the compound of formula (III) to the compound of formula (II), for example between 1.01 and 1.08 mole equivalents of the compound of formula (III), preferably 1.05 mole equivalents.

The reaction is preferably performed at a temperature between ambient and 100°C, for example between ambient and about 60°C.

Suitable bases for use in the process of the invention include organic bases such as triethylamine, diisopropylamine, pyridine, N,N-dimethylaniline, N,N-dimethylaminopyridine, 1,8-diazabicyclo[4.3.0]undec-7-ene and 1,4-diazabicyclo[2.2.2]octane, and tetraalkylammonium hydroxides, e.g. a tetraC₁₋₆alkyl alkylammonium hydroxide such as tetrabutylammonium hydroxide or tetramethylammonium hydroxide. Inorganic bases such as sodium and potassium hydrogen carbonate, sodium and potassium hydroxide and sodium and potassium carbonate may also be used.

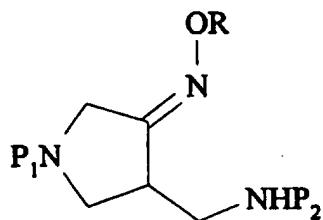
The base is preferably triethylamine.

Suitably between 3.2 and 3.8 mole equivalents of base are used based on the compound of formula (II), preferably 3.4 mole equivalents of base are used. When the base is a tetraalkylammonium hydroxides then the process may use less than 3 equivalents, e.g. about 2.6 equivalents, of the base.

Suitable leaving groups X in the compound of formula (II) include halogens, particularly chlоро, other suitable leaving groups will be apparent to those skilled in the art.

The compound of formula (III) is preferably in the form of the dimethanesulfonate salt, e.g. 4-aminomethyl-3-methoxyiminopyrrolidinium dimethanesulfonate. Other salts of the compound of formula (III) include the hydrochloride, trifluoroacetate and sulfate salts.

Dimethanesulfonate salts of the compound of formula (III) may be produced by a process comprising reaction of a compound of formula (IV):



(IV)

wherein R is as defined for formula (I) and P_1 and P_2 , which may be the same or different, are amino protecting groups, with methanesulfonic acid.

Suitable protecting groups P_1 and P_2 include any suitable amino protecting groups which are removable by treatment with methanesulfonic acid. The preferred protecting group for both P_1 and P_2 is t-butoxycarbonyl.

The reaction of the compound of formula (II) and methanesulfonic acid is suitably carried out at a temperature between about 10°C and about 50°C, more preferably at a temperature of 40-45°C.

The amount of methanesulfonic acid used to effect the deprotection of the compound of formula (II) is suitably 2 to 4 equivalents. For example, 2.4 equivalents, suitably used at a temperature of between 35°C and 40°C; or 3 equivalents, suitably

used at ambient temperature. More preferably 2.5 equivalents used at a temperature of 40-45°C.

The reaction is suitably carried out in a solvent, for example, an alcohol such as methanol, ethanol, isopropanol, or n-propanol, dichloromethane, acetonitrile, acetone, methyl iso-butyl ketone, DME, THF, tert-butylmethyl ether, dioxane or ethyl acetate or a mixture of any of these. The solvent is preferably methanol. Suitably, up to 10 equivalents by volume of solvent may be used, e.g. about 4 equivalents.

The compounds of formula (II), (III) and (IV) may be prepared by the processes described in US 5,633,262, EP 688772 and PCTIKR99/00099.

The compound of formula (I) produced according to the invention is preferably (R,S)-7-(3-aminomethyl-4-syn-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-riaphthyridine-3-carboxylic acid methanesulfonate or a hydrate thereof, preferably the sesquihydrate, as disclosed in WO 98/42705. The methanesulfonate and hydrates thereof may be synthesised from the free acid as described in WO 98/42705 and WO 00/17 199.

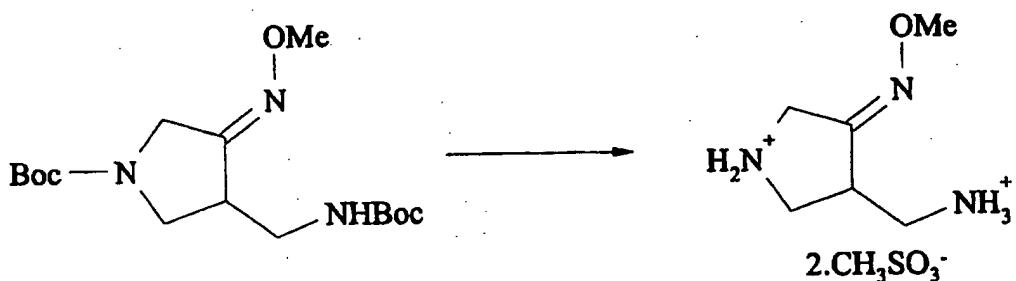
The process of the invention has the advantages that it produces drug substance of superior quality compared to the known process using dry acetonitrile as solvent. In addition the use of an aqueous solvent is more cost effective and may offer environmental advantages.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The invention is illustrated by the following examples. However, it should be understood that the examples are intended to illustrate but not in any manner limit the scope of the invention.

Example 1

Synthesis of 4-aminomethyl-3-methoxyiminopyrrolidinium dimethanesulfonate



A solution of 1 -(N-t-butoxycarbonyl)-4-(t-butoxycarbonylaminomethyl)pyrrolidin-3-methoxime (100g) in methanol (660mL) at 15-20°C under nitrogen was treated with methanesulfonic acid (56.4mL) over 5 min keeping the temperature below 30°C. The solution was stirred at 20-25°C for 16-20hrs. During this time the product precipitated forming a thick suspension. The product was isolated by filtration, washed with methanol (165ml) and dried under vacuo at 25°C to give the title compound 84g (86%).

m.p. 189-193°C;

m/z: 144 (M+H)⁺

¹H NMR (400MHz, d₆-DMSO) δ: 9.27, (2H, brs), 7.95 (3H, brs), 4.01 (1H, d), 3.92 (1H, d), 3.87 (3H, s), 3.69 (1H, m), 3.26 (2H, m), 3.26 (2H, m), 3.15 (1H, m), 3.08 (1H, m), 2.39 (6H, s);

Analysis: C, 28.64%, H, 6.25%, N, 12.46%; $C_8H_{21}N_3O_7S_2$ requires C, 28.65%, H, 6.31%, N, 12.53%.

Example 2

Synthesis of 4-aminomethyl-3 -methoxyiminopyrrolidinium dimethanesulfonate

A solution of 1-(N-t-butoxycarbonyl)-4-(t-butoxycarbonylaminomethyl) pyrrolidin-3-methoxime (100 g) in methanol (400mL) at 20°C under nitrogen was treated with methanesulfonic acid (47mL, 70g, 2.5 equiv) over 15 min keeping the temperature below 25°C. The solution was heated to 40-45°C over 30 mins and maintained at this temperature for 4-5 hrs. During this time the product precipitated forming a thick suspension. The crude product was isolated by filtration under nitrogen and washed with methanol (200mL). The crude product was suspended in methanol (4 volumes, approx. 360mL) and heated to reflux for 1 hr. After cooling to 20°C the suspension was stirred for 1 hour. The product was filtered, washed with methanol (2 volumes, approx. 180ml) and dried under vacuum at 40°C to give the title compound 73.8g (78%).

Characterising data were consistent with a standard sample of the title compound.

Example 3

Synthesis of (R,S)-7-(3-aminomethyl-4-syn-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid

Triethylamine (5.1 ml) was added to 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (3 .05g) in water (25ml) at 15-20°C and the mixture stirred for 20 min. 4-Aminomethyl-3-methoxyimino-pyrrolidinium

dimethanesulfonate (3.86g) was added, followed by water (5ml), and the mixture stirred at 20-25°C for 17½ hours. The resulting product was filtered and the cake washed with water (30ml) followed by ethanol (30ml) and dried under vacuum at 50°C to give the title compound as a white solid (4.23g). (102% as is, 86% on assay). Characterising data were consistent with a standard sample of the title compound.

Example 4

Synthesis of (R,S)-7-(3-aminomethyl-4-syn-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid

Triethylamine (34ml) was added to 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (20.17g) in a mixture of acetonitrile (100ml) and water (100ml) at 15-20°C and the mixture stirred for 30 mm. 4-Aminomethyl-3-methoxyiminopyrrolidinium dihydrochloride (18.9g) was added, followed by water (5ml), and the mixture stirred at 20-25°C for 23½ hours. The resulting product was filtered and the cake washed with ice-cold 1:2 acetonitrile:water (100ml) followed by acetonitrile (100ml), air dried, then dried under vacuum, at ambient temperature, to give the title compound as a fawn solid (26g). (94% as is, 78.8% on assay). Characterising data were consistent with a standard sample of the title compound.

Example 5

Synthesis of (R,S)-7-(3-aminomethyl-4-syn-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid

A 40% solution of tetrabutylammonium hydroxide in water (15 ml, 23 mmol) was added to a mixture of 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (2.5 g, 8.8 mmol) and 4-amino-methyl-3-methoxyiminopyrrolidinium dimethanesulfonate (3.12 g, 9.3 mmol) in water (8 ml) at 20 - 25°C and the mixture stirred for 24 hours. The resulting product was filtered and the cake washed with water (25 ml) followed by ethanol (25 ml) and dried under vacuum at 50°C to give the title compound as a white solid (3.47 g). Characterising data were consistent with a standard sample of the title compound.

Example 6

Synthesis of (R,S)-7-(3-aminomethyl-4-syn-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate

A solution of methanesulfonic acid (0.33 g, 3.43 mmol) in dichloromethane (1 ml) was added to a suspension of (R,S)-7-(3-aminomethyl-4-syn-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (1.5 g at 89.9% purity, 3.46 mmol) in a mixture of dichloromethane (23.2 ml) and ethanol (2.7 ml) at 30°C. The mixture was stirred at 30°C for 3 hours then cooled to 20°C and filtered. The cake was washed with dichloromethane (20 ml) and dried at 50°C under vacuum to give the title compound (1.71 g) (102% as is, 91% on assay). Characterising data were consistent with a standard sample of the title compound.

Example 7

Synthesis of (R,S)-7-(3-aminomethyl-4-syn-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate

(R,S)-7-(3-aminomethyl-4-syn-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate (27.5 g at 91% purity, 51.4 mmol) was stirred in a mixture of isopropanol (150 ml) and water (75 ml) and heated until a clear solution was obtained (52°C). The solution was cooled to 34°C and seed crystals of (R, S)-7-(3 -aminomethyl-4-syn-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate added. The resulting suspension was allowed to cool to 25°C over 1 hour and stirred for 18 hours. The slurry was cooled to 0 - 4°C, stirred for 2 hours, then filtered and the cake washed with isopropanol (30 ml). The product was sucked dry for 2 hours and then further dried at 50°C under vacuum. The dried product was exposed to the atmosphere to give the sesquihydrate, 22.9 g (92%). Characterising data were consistent with a standard sample of the title compound.